

**ARSENIC COMPOUNDS, INORGANIC\***  
First Listed in the *First Annual Report on Carcinogens*

**CARCINOGENICITY**

Inorganic arsenic compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans (IARC S.7, 1987) (See Inclusion of Substances in the Introduction for a discussion of carcinogenicity of metals). Many cases of skin cancer have been reported among people exposed to arsenic through medical treatment with inorganic trivalent arsenic compounds. In some instances, skin cancers have occurred in combination with other cancers, such as liver angiosarcoma, intestinal, and urinary bladder cancers and meningioma. Epidemiological studies of cancer after medical treatment with arsenic have shown an excess of skin cancers, but no clear association with other cancers has been obtained. No relation was found between prostatic cancer and treatment of syphilis with arsenicals. An association between environmental exposure to arsenic through drinking water and skin cancer has been observed and confirmed. Epidemiological studies in areas where drinking water contained 0.35 to 1.14 mg/L arsenic elevated risks for cancers of the bladder, kidney, skin, liver, lung, and colon in both men and women. Occupational exposure to inorganic arsenic, especially in mining and copper smelting, has quite consistently been associated with an increased risk of cancer. An almost tenfold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic, and relatively clear dose-response relationships have been obtained with regard to cumulative exposure. Other smelter worker populations have been shown to have consistent increases in lung cancer incidence, as well as increases of about 20% in the incidence of gastrointestinal cancer and of 30% for renal cancer and hematolymphatic malignancies. The observation in an earlier study of an increase in lung risk among a population of smelter workers has been confirmed, with a risk of sixfold to eightfold among roasters. With regard to histological type of lung cancer, a significant, relative excess of adenocarcinomas and a slight excess of oat cell cancers were seen among smelter workers.

An IARC Working Group reported that there is limited evidence of carcinogenicity of inorganic arsenic compounds in experimental animals (IARC V.2, 1973; IARC V.23, 1980; IARC S.4, 1982; IARC S.7, 1987). When injected subcutaneously during the first 3 days of life into mice whose mothers had been injected subcutaneously once during gestation, arsenic trioxide induced lung adenomas. When administered by intratracheal instillation, arsenic trioxide induced low incidences of carcinomas, adenomas, papillomas and adenomatoid lesions of the respiratory tract in hamsters of both sexes. It induced a low incidence of adenocarcinomas at the site of its implantation into the stomach of rats. A high incidence of lung carcinomas was induced in rats after a single intratracheal instillation of a pesticide mixture containing calcium arsenate. Intratracheal instillations of calcium arsenate into male hamsters resulted in a borderline increase in the incidence of lung adenomas, whereas no such effect was observed with arsenic trisulfide. When administered in the drinking water, sodium arsenite enhanced the incidence of renal tumors induced in male rats by intraperitoneal injection of *N*-nitrosodiethylamine.

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\* There is no separate CAS registry number for arsenic compounds, inorganic.

## PROPERTIES

Arsenic and certain arsenic compounds occur in crystalline, powder, amorphous, or vitreous forms. Elemental arsenic is not soluble in water; calcium arsenate and calcium arsenites (1:1), (2:1), and (2:3) are sparingly soluble in water; the remaining arsenicals are soluble in water. Arsenic pentoxide, potassium arsenite, and the three sodium salts are soluble in ethanol. Arsenic, arsenic pentoxide, arsenic trioxide, the calcium arsenites, lead arsenate, and potassium arsenate are soluble in various acids. When heated to decomposition, arsenic compounds emit toxic arsenic fumes.

Arsenic is available in a technical grade (99% pure) and in a high-purity grade (99.999+% pure) which is intended for semiconductor use. Arsenic pentoxide, sodium arsenite, sodium arsenate, potassium arsenate, and potassium arsenite are available in technical and chemically pure grades. Potassium arsenite is also available in a 1% aqueous solution commonly known as Fowler's solution. Arsenic trioxide can be purchased in a 95% crude grade, in a 99% pure refined grade, as a 1% solution in approximately 5% hydrochloric acid, in 2-mg tablets, and as a paste. Calcium arsenate is available as pure grade with 99% purity or as a grade containing 61% calcium arsenate, 9% calcium arsenite, and an excess of lime and calcium carbonate. Lead arsenate is available as acid lead arsenate containing 33% arsenic pentoxide, as a wettable powder (94-98% pure), as a dust, and as a paste.

## USE

The estimated end-use distribution of arsenic in 1990 was 70% in wood preservatives, 22% in agricultural chemicals (principally herbicides and desiccants), 4% in glass, 2% in nonferrous alloys and 2% in other uses (USDOL, 1991). Metallic arsenic was used in nonferrous alloys and in the electronics industry for semiconductor materials. Arsenic pentoxide, calcium arsenate, lead arsenate, and sodium arsenate are used in the formulation of wood preservatives. There is an increased use of arsenic trioxide by the wood preservative industry due to its use in formulating chromated copper arsenate (USDOL, 1987). Calcium arsenate is used as an insecticide on cotton and against certain soil insects, as an herbicide for treating turf and lawns to control weeds, and as a pesticide on fruits and vegetables. Sodium arsenate is used in ant killers and in animal dips as an insecticide. Sodium arsenite is used in low percentages in herbicides for ant control and weed control, for destroying trees and stumps, in animal dips, in pesticide baits, and for soil treatment against termites. Although there is no present commercial use for calcium arsenite (1:1), it was formerly used as an insecticide, pesticide, and molluscicide. Lead arsenate was originally a part of insecticide formulations, though this use is currently negligible. Arsenic, arsenic trioxide, lead arsenate, and potassium arsenite are used in various medicines, mostly veterinary. Formerly, disodium hydrogen arsenate was also used in this capacity. Potassium arsenite as Fowler's solution is a hematinic used as a temporary medication for the treatment of myelogenous leukemia and certain skin lesions. The use of Fowler's solution as a veterinary medicine is not generally deemed acceptable for widespread use. Arsenic (including metallic arsenic), arsenic pentoxide, and arsenic trioxide are used as alloying additives, particularly with lead and copper. Arsenic and arsenic trioxide are also used in the manufacture of low-melting glasses. High-purity arsenic metal is used in the electronics industry for semiconductor materials. There is no present commercial use for potassium arsenate, although it has been used in fly baits, hide preservation, and textile printing and as a lab reagent. Arsenic trioxide is the source for 97% of all arsenic products (IARC V.2, 1973; IARC V.23, 1980).

## PRODUCTION

In 1996, the United States was the largest consumer of arsenic, accounting for almost two-thirds of world demand, and its demand for arsenic metal and compounds has averaged about 4.4 million lb for the past four years (Edelstein, 1997). In 1985, the sole domestic producer of arsenic ceased operation, resulting in the United States becoming completely dependent upon foreign suppliers. This dependency is anticipated to continue indefinitely (USDOL, 1988). Arsenic trioxide is imported and then converted to arsenic acid by three major companies, one headquartered in the United States and two headquartered in the United Kingdom. Imports of arsenic acid, therefore, have seen a decline in recent years. In 1996, only 2,205 lb were imported, whereas in 1995 less than 1,100 lb were imported. These are very low values when compared to the 88,185 lb imported in 1992 (Edelstein, 1997). In 1994, 11,023 lb of the acid were imported.

In 1985, the final year of production, 4.8 million lb of arsenic, reported as arsenic trioxide containing 76% arsenic by weight, were produced. In 1984, 14.9 million lb of arsenic were produced. Domestic production in 1983 and 1982 totaled 16.1 and 17.6 million lb, respectively (USDOL, 1988, 1987).

Imports of arsenic metal averaged 1-2 million lb over the period of 1982-1996. Imports of arsenic trioxide increased from 32 million lb to 64 million lb over the same time period (Edelstein, 1997 and USDOL, 1987, 1988, 1990, and 1991).

There are single producers of calcium arsenate and potassium arsenate, two producers of lead arsenate, and four producers of sodium arsenite, with no reported production volumes. Production of potassium arsenite is believed to be limited to a very small quantity produced by a few companies (IARC V.23, 1980). The Bureau of Mines has reported the amount of arsenic compounds imported and exported for the years covering 1982 through 1989. References to arsenic compounds include arsenic acid, sodium arsenate, lead arsenate, and miscellaneous compounds. In 1989, the United States imported 132,000 lb of arsenic acid (USDOL, 1990).

## EXPOSURE

The primary routes of potential human exposure to arsenic and certain arsenic compounds are inhalation, ingestion, and dermal contact. NIOSH estimated that 1.5 million industrial workers are potentially exposed to arsenic and its compounds during manufacturing and processing operations. The National Occupational Exposure Survey (1981-1983) indicated that 36,194 total workers, including 4,007 women, are potentially occupationally exposed to arsenic, arsenic pentoxide, arsenic trioxide, or sodium arsenite (NIOSH, 1984). Higher than average worker exposure may occur during the smelting of ores containing arsenic, during pesticide application, and wood preservation (NIOSHb, 1979). ACGIH has adopted a threshold limit value (TLV) of 0.01 mg/m<sup>3</sup> for arsenic and soluble compounds, as arsenic, as an 8-hr time-weighted average (TWA) (ACGIH, 1996). Recent reductions in emissions and improved industrial hygiene practices have substantially reduced occupational exposures. Since many uses for arsenical pesticides have been banned and since arsenic production no longer occurs in the United States, the number of workers has likely decreased since the early 1980s.

Direct consumer exposure to arsenic and arsenic compounds may occur through consumption of foods. Food provides an average intake of about 46 µg of arsenic per person per day. The highest levels are detected in seafood, meats, and grains. Trace levels of arsenic have been reported in the tissue of livestock that were administered arsenic drugs and feed additives.

Potential consumer exposure to arsenic also occurs through the consumption of drinking water contaminated with arsenical pesticides, natural mineral deposits, or improperly disposed arsenical chemicals (ATSDR, 1993-K004). In the United States mostly communities in the western and southwestern states and Alaska, where one or more small water systems are used, are areas having relatively high arsenic concentrations in drinking water; one of the largest populations is Hanford, California (Chappell et al., 1997).

An investigation on the excretion of arsenic in breast milk of lactating women living in an environment with high concentrations of arsenic in the drinking water (about 200 µg/L) found high concentrations of arsenic in maternal blood (10 µg/L, total arsenic) and maternal urine (320 µg/L, metabolites of inorganic arsenic) versus previous values found for subjects without known exposure to the metal (1 to 2 µg/L and about 10 µg/L, respectively) (Concha et al., 1998). However, the study failed to observe a correlation between these concentrations and the concentrations of arsenic found in breast milk, which were low, averaging about 2 µg/kg. This low rate of arsenic excretion in milk was seen in the low levels of arsenic detected in the urine of two nursing babies. Therefore, in areas with high concentrations of arsenic exposure, a long breast-feeding period can prevent a child from being exposed to arsenic during the first period of life.

Additionally, the general population is potentially exposed to arsenic compounds through air emissions from pesticide manufacturing facilities, smelters, cotton gins, glass manufacturing operations, cigarette tobacco, burning of fossil fuels, and other sources (ATSDR, 1993-K004). Arsenic used as color pigments in paints can also be ingested by contamination of hands, fingernails, food, cups, cigarettes, and by holding paint brushes in the mouth (HSDB, 1997). The Toxic Chemical Release Inventory (EPA) listed 72 industrial facilities that produced, processed, or otherwise used arsenic in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of arsenic to the environment which were estimated to total 192,000 lb. EPA estimates that more than six million people residing within a 12-mile radius of major sources of copper, zinc, and lead smelters may be exposed to 10 times the average U.S. atmospheric levels of arsenic (HSDB, 1997). The use of topical arsenic medications may also potentially expose a limited portion of the population to arsenic and arsenic compounds.

## **REGULATIONS**

CPSC regulates arsenic sulfide, arsenates, and arsenites by prohibiting the presence of any of the chemicals in fireworks devices. EPA regulates arsenic and certain arsenic compounds under the Clean Air Act (CAA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Arsenic emissions from smelters and other facilities are regulated under CAA. CWA has established effluent guidelines controlling the environmental release of arsenic compounds for certain industrial categories. Reportable quantities (RQs) have been established under CERCLA and CWA for arsenic (1 lb) and certain arsenic compounds (arsenic pentoxide, arsenic trioxide, and lead arsenate, 5000 lb; calcium arsenate, calcium arsenite, potassium arsenite, sodium arsenate, and sodium arsenite, 1000 lb). Under RCRA, EPA regulates arsenic as a hazardous constituent of waste. SDWA limits arsenic in drinking water to a maximum level of 0.05 mg/L. SARA has established threshold planning quantities (TPQ) for some arsenic compounds and subjects arsenic and arsenic compounds to reporting requirements. FDA enforces tolerances set by EPA under FD&CA for residues of pesticides containing arsenic in fruits and vegetables, field crops, and livestock. FDA has also set tolerance limits for the

residue of arsenic compounds when used as veterinary drugs and in the feed and drinking water of animals, as well as food and color additives and bottled water. Based on evidence of carcinogenicity in humans, NIOSH recommends a ceiling limit of  $2 \mu\text{g}/\text{m}^3$  (15 min.) for arsenic and inorganic compounds, as arsenic (NIOSHc, 1996). OSHA regulates arsenic and certain arsenic compounds under the Hazard Communication Standard and as chemical hazards in laboratories. OSHA has promulgated a final standard of  $10 \mu\text{g}/\text{m}^3$  for occupational exposure to inorganic arsenic compounds. Additionally, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls. A permissible exposure limit (PEL) of  $0.5 \text{ mg}/\text{m}^3$  for organic arsenic as an 8-hr TWA also has been adopted by OSHA. Regulations are summarized in Volume II, Table A-5.